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August 27, 1997

Mr. Carl Blair
Agency for Toxic Substances & Disease Registry
Atlanta Federal Center - 10th Floor
61 Forsyth Street, S.W.
Atlanta, GA 30303

Dear Mr. Blair:

We understand that you will be performing a health assessment for toxaphene relative to the Terry Creek and Dupree Creek areas in Brunswick, Georgia. For your use in performing the health assessment, enclosed are several reports and publications of recently developed toxicology information on toxaphene. This information affects the evaluation of effects seen in laboratory animals for human risk from exposure to toxaphene. As the enclosed documents demonstrate, the formation of tumors in rats and mice that led to the classification of toxaphene as a probable human carcinogen occur by mechanisms that have little or no relevance to humans.

Based, in part, on the findings of increased incidences of rat thyroid follicular cell carcinomas and adenomas and mouse hepatocellular carcinomas in a National Cancer Institute Carcinogenesis Bioassay [National Cancer Institute Carcinogenesis Technical Report Series No. 37, 1979, DHEW Publication No. (NIH) 79-837], toxaphene was classified by the U. S. Environmental Protection Agency as a probable human carcinogen. It is now known that the development of thyroid tumors in rats and liver tumors in mice can often occur by mechanisms that have little or no relevance to humans. The recently completed studies were conducted to determine whether the mechanisms involved in the development of these tumors in laboratory animals are relevant to human risk assessment. As stated above, the studies did demonstrate that the mechanisms involved in the development of these tumors have little or no relevance to humans. Therefore, these animal tumors should have little or no bearing on assessments of the impact of exposure to toxaphene to human health.

Many of these documents were previously submitted to Dr. William Cibulas, Chief, Research Implementation Branch, Division of Toxicology, ATSDR, under Docket Control Number ATSDR-42, in June, 1996 in response to an ATSDR Federal Register notice. Since that time, manuscripts have been submitted to peer-review journals for some of the studies. One of these manuscripts has been published. Copies of these manuscripts are also included in this package.

The documents in the enclosed three-ring binder are:

Tab 1. A report of a 28-day study conducted with rats orally dosed with toxaphene to determine the effect of toxaphene on thyroid function (Huntingdon Life Sciences, Inc., 1996). This study demonstrates that the oral administration of toxaphene to rats leads to increases in thyroid stimulating hormone (TSH) and subsequently to increased colloid content and hypertrophy and hyperplasia of thyroid follicular cells. The increase in TSH and the stimulation of the thyroid gland can lead to thyroid tumors in rats; however, this is not known to occur in humans. The results of the study were presented at the 1996 annual meeting of the Society of Toxicology.

Tab 2. A reprint of the publication, "Thyroid Function and Thyroid Tumors in Toxaphene-Treated Rats" (R. S. Waritz, et al.), based on the above study. The publication is from the peer-review journal *Regulatory Toxicology and Pharmacology*, volume 24, pages 184-192 (1996).

Tab 3. A report of preliminary findings of a study conducted by the Environmental and Occupational Health Sciences Institute (EOHSI), Robert Wood Johnson Medical School. In this study oral administration of toxaphene to mice caused an increase in hepatic microsomal cytochrome P-450, but not in CYP 4A1, an indicator of peroxisome proliferation. Preliminary analysis of hepatic DNA adduct levels indicates that toxaphene did not induce adduct formation and, therefore, may not cause liver tumors in mice through an effect on genetic material.

Tab 4. A manuscript, "Investigation of Hepatic Cytochrome P450 Enzyme Induction and DNA Adduct Formation in Male CD/1 Mice Following Oral Administration of Toxaphene" (C. C. Hedli, et al.) based on the above EOHSI study. The manuscript has been submitted to the peer-review journal, *Journal of Applied Toxicology*.

Tab 5. A report from Experimental Pathology Laboratories, Inc. (1996), of a Pathology Working Group Peer Review of the neoplastic lesions in the livers of mice from the National Cancer Institute Bioassay of toxaphene. The Pathology Working Group Peer Review was performed in order to obtain a consensus diagnosis of the lesions based on current diagnostic criteria.

Tab 6. A statistical anaysis of the Pathology Working Group Peer Review concludes that, although there was an increase in benign liver tumors in the male and female mice, there was no increase in malignant liver tumors in either sex.

Tab 7. Although not statistically significant, the National Cancer Institute bioassay

reported that kidney tumors were seen in rats. The report of Dr. James A. Swenberg, University of North Carolina, (1995) states that kidneys of rats receiving toxaphene in the diet contain hyalin droplets which stain positively for alpha$_{2u}$-globulin. Alpha$_{2u}$-globulin nephropathy is a disease that has been found to be specific for the rat and to have no relevance to human risk assessment.

Tab 8. Recently, toxaphene has been reported to have estrogenic effects when tested using an *in vitro* system. Bioqual, Inc. (1994) reports on a study in which ovariectomized rats were treated orally with toxaphene. The study demonstrates that toxaphene is not estrogenic in the whole animal based on lack of cornification of vaginal cells.

Tab 9. A second study to determine the estrogenic effects of toxaphene was performed using the oral administration of several doses of toxaphene. Bioqual, Inc. (1997) reports on this study which demonstrates that toxaphene may have weak estrogenic activity in the whole animal based on increases in uterine weights in rats treated with extremely high doses of toxaphene. These doses caused systemic toxicity and deaths of some of the animals. It was also noted in this study that there was a lack of cornification of vaginal cells.

Tab 10. A manuscript, "Evaluation of Toxaphene for Estrogenic Activity in the Ovariectomized Adult Rat Using a Seven-day Vaginal Cornification/Uterine Weight Bioassay" (J. R. Reel, et al.). The manuscript has been submitted to the peer-review journal, *Fundamental and Applied Toxicology.*

These newer data allow a better understanding of the mechanisms of the toxicity seen in laboratory animal studies and, thus, allow a better interpretation of the relevance of findings from *in vitro* and animal studies to human risk assessment. This is demonstrated in an evaluation of all of the toxicity information for toxaphene, including the newly developed data, that was prepared by Jellinek, Schwartz & Connolly, Inc. Based on this information, a petition was submitted to the U.S. EPA and a meeting was held with representatives of the EPA Office of Solid Waste, the Office of Pesticide Programs and the Office of Research and Development. A formal document is being prepared, based on guidance provided to Hercules by EPA at that meeting. This document will be provided to EPA by the first week in October, 1997.

A copy of the Jellinek, Schwartz & Connolly report, "Toxaphene: A Basis for a Change in the Cancer Classification and for a Change in and Recalculation of the Cancer Potency Factor", dated February 18, 1997, is also enclosed for your information. Copies of this report were previously provided to Drs. Frank Schnell and A. S. Susten, Division of Health Assessment and Consultation, ATSDR.

In addition, Jellinek, Schwartz & Connolly, Inc. and Sielken, Inc. having determined that there is a basis for changing the cancer potency factor (slope factor) for toxaphene, have prepared a document presenting the justification for the change. Based on their determination, they have recalculated the potency factor. This report, "Toxaphene: Basis for a Change in and Recalculation of the Cancer Potency Factor", dated August 21, 1997, is included in the three-ring binder under Tab 11. The first 9 pages of this report present the justification for changing the potency factor; the remainder of the report, i.e., Appendix 1, presents the calculation of a new potency factor.

Using both the current EPA slope factor [1.1 $(mg/kg/day)^{-1}$] and the recalculated slope factor [0.16 $(mg/kg/day)^{-1}$], soil cleanup levels for toxaphene in a residential scenario with a child receptor using oral and dermal exposure pathways have been calculated using current EPA guidelines. These cleanup levels are 6.7 ppm and 46.0 ppm, using the current and recalculated slope factors, respectively. The exposure assumptions and variables used in calculating these cleanup levels are presented in the Jellinek, Schwartz & Connolly document, "Calculation of New Toxaphene Cleanup Level for Future Residential Use" (August 25, 1997). This document is included in the three-ring binder under Tab 12.

If you have any questions, please contact us.

Sincerely,

Timothy D. Hassett
Staff Environmental Engineer

Enclosures

cc: without enclosures
Leo Francendese - U. S. EPA Region 4
Annie M. Godfrey - U. S. EPA Region 4
Paul Peronard - U. S. EPA Region 4
Kathleen A. Morgan - U. S. Army Corps of Engineers
Randall O. Manning, Ph.D. - Georgia EPD